Chronic myeloid leukemia: Evolving from fatal stem cell disease to cure

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2015

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CHAPTER 5

Imatinib discontinuation in chronic phase myeloid leukaemia patients in sustained complete molecular response: a randomised trial of the Dutch-Belgian Cooperative Trial Group for Haemato-Oncology (HOVON)

Eur J Cancer 2013;49(15):3242-3246

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ABSTRACT

Background: Tyrosine kinase inhibitors treatment in responding chronic myeloid leukaemia (CML) patients is generally continued indefinitely. In this randomised phase II trial, we investigated whether CML patients in molecular response$^{4.5}$ (MR$^{4.5}$, by quantitative reverse-transcription polymerase chain reaction (RQ-PCR)) after previous combination therapy with imatinib and cytarabine may discontinue imatinib treatment safely.

Patients and methods: Thirty-three patients from the HOVON 51 study with an MR$^{4.5}$ for at least 2 years who were still on imatinib treatment were randomised between continuation of imatinib (arm A, *n* = 18) or discontinuation of imatinib (arm B, *n* = 15).

Results: After a median follow up of 36 months since randomisation, 3 patients (17%) in arm A and 10 patients (67%) in arm B had a molecular relapse. All 3 relapsing patients in arm A had also stopped imatinib after randomisation. All but one relapsing patient relapsed within 7 months after discontinuation of imatinib. The molecular relapse rate at 12 and 24 months after randomisation was 0% and 6% (arm A) and 53% and 67% (arm B) respectively. As-treated analysis revealed 56% and 61% relapses at 1 and 2 years since cessation in patients who discontinued imatinib, in contrast to 0% of patients who continued imatinib. All evaluable patients remained sensitive to imatinib after reinitiation and regained a molecular response.

Conclusion: Our data suggest that discontinuation of imatinib is safe in patients with durable MR$^{4.5}$. This study is registered at www.clinicaltrials.gov (NCT00028847).

INTRODUCTION

The introduction of imatinib, a decade ago, has dramatically improved the outlook of chronic myeloid leukaemia (CML) patients. In the International Randomised Study of Interferon versus STI571 (IRIS study), high rates of haematologic, cytogenetic and molecular responses were seen. Moreover, an impressive reduction of patients progressing to more advanced stages of the disease was observed.[1,2]

Until now, responding patients are supposed to continue tyrosine kinase inhibitors (TKIs) indefinitely. Nevertheless, several studies have recently shown that around 40% of the patients with a long-lasting deep molecular response or undetectable *BCR-ABL1* can stop imatinib without subsequent molecular relapse.[3-6] In addition, published studies suggest that all relapsing patients are sensitive to imatinib reinitiation.[3,5,7-9]

These observations justified an amendment to our previously published feasibility and efficacy study of imatinib in combination with cytarabine.[10,11] In this HOVON 51 study 162 patients were treated with escalating doses of imatinib and cytarabine, a combination hypothesised to result in deeper molecular responses. Indeed, a relatively high cumulative $MR^{4.5}$ rate of 53% at 5 years was achieved.[10,11] We set out to investigate if these deeper molecular responses would translate in higher chances of remaining in remission after discontinuation of imatinib. Thus, we here report on an amendment of the HOVON 51 study, randomising patients with a durable $MR^{4.5}$ between imatinib continuation or discontinuation.

PATIENTS AND TREATMENT

In the HOVON 51 study, patients received escalating doses of imatinib (200, 400, 600 or 800 mg) in combination with escalating doses of cytarabine (200 or 1000 mg/m^2 days 1-7 during two cycles) according to the study protocol. Imatinib maintenance consisted of imatinib 400, 600 or 800 mg. The study protocol and results have previously been published.[10,11] Patients were eligible for randomisation between continuation or stopping imatinib when they had attained a $MR^{4.5}$ on protocol for at least 2 years. $MR^{4.5}$ was defined as >4.5 log reduction of *BCR-ABL1* by quantitative reverse-transcription polymerase chain reaction (RQ-PCR) and confirmed by a negative real-time polymerase chain reaction (RT-PCR). Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The ethics committees of the participating institutions approved the study.

Patients were centrally randomised 1:1 between both arms. Patients randomised to discontinue imatinib immediately stopped imatinib. Following discontinuation of imatinib patients underwent monthly RQ-PCR for *BCR-ABL1* on peripheral blood and 2-monthly RQ-PCR for *BCR-ABL1* on bone marrow during the first half year. After the first 6 months peripheral blood and bone marrow testing were performed every 2 and 3 months respectively, until 1 year after discontinuation. Thereafter, RQ-PCR for *BCR-ABL1* was performed

on peripheral blood every 3 months and on bone marrow every 6 months. Cytogenetic evaluations were performed at 2, 4 and 6 months and at 3 months intervals thereafter until 1 year after discontinuation, thereafter at least every 6 months. Patients randomised to continue imatinib underwent peripheral blood RQ-PCR for *BCR-ABL1* every three months indefinitely. According to the original HOVON 51 protocol, bone marrow cytogenetics was performed every 6 months during the first year and once a year thereafter.
In case the RQ-PCR for *BCR-ABL1* result became positive (i.e. <4.5 log reduction) in patients who had stopped imatinib, this was confirmed by a second RQ-PCR for BCR-ABL1. When this second PCR was also positive, patients restarted imatinib maintenance therapy in the same dose as they had received before discontinuation of the drug. For the HOVON 51 design and flow diagram of this study we refer to the Supplemental Files 1 and 2.

METHODS

The molecular response was centrally assessed at the Erasmus University Medical Centre in Rotterdam using *BCR-ABL1* real-time quantitative reverse-transcription polymerase chain reaction (RQ-PCR). RQ-PCR was performed as previously published.[10,11] A laboratory-specific conversion factor to the international scale (IS) was acquired via the European Treatment and Outcome Study (EUTOS) for CML.[12] The quality of the *BCR-ABL1* real-time quantitative PCR quantification was monitored by the Dutch Network for Molecular Diagnostics of Haematologic malignancies (MODHEM, website www.modhem.nl) by means of annual quality control rounds.
Definitions of molecular responses are as described previously.[10]

DEFINITION OF END-POINTS AND STATISTICAL CONSIDERATIONS

The primary objective of the study was to evaluate whether patients in a long lasting MR$^{4.5}$ after induction with cytarabine and imatinib maintenance treatment could discontinue imatinib safely.
The primary end-point of this study was the molecular relapse rate at 6 months after discontinuation for patients in arm B. Our aim was to estimate the 6-months' molecular relapse rate with a standard error of 10%, for which 25 patients in arm B would be required. Patients were randomised 1:1. Therefore 25 patients would also be included in arm A. The study was not designed nor powered to compare the results between the two treatment arms. Secondary end-points were the rate and time to complete molecular response after resuming imatinib in patients with a molecular relapse after discontinuation, the rate of progression to haematological relapse and progression to accelerated phase and blast crisis in patients who discontinued imatinib. All analyses were performed according to the intention-to-treat principle. For reasons of clarity, results of a per-protocol analysis are also given.
The molecular relapse rate at 6 and 12 months was estimated per treatment arm using the actuarial method of Kaplan and Meier, and the corresponding 95% confidence interval (CI) was calculated. A Kaplan-Meier curve was generated to illustrate molecular relapse over time.

RESULTS

The results of the HOVON 51 study have been described previously.[10,11] Of 162 included patients, 33 patients from nine centres with persistent MR$^{4.5}$ were enrolled in this stop study between August 2008 and April 2011. Eighteen patients were randomised to continue imatinib therapy (arm A) and 15 patients were randomised to discontinue imatinib therapy (arm B). The randomisation was continued until 2011, when the results of the other stop studies became available and an amendment of the protocol was accepted wherein all patients in long-lasting MR$^{4.5}$ were allowed to stop imatinib. Therefore we did not include 50 patients as outlined in our previous statistical plan. The data were analysed as available at April 2013. Median follow-up since randomisation is 36 months (range 8-54). Patient characteristics are shown in Supplemental File 3. Median time to reach MR$^{4.5}$ was 20 months. Until now, 3 patients (17%) in arm A and 10 patients (67%) in arm B experienced a molecular relapse (Figure 1). All patients relapsing in arm A (at 9, 13 and 20 months after randomisation) had discontinued imatinib already. The time elapsed between stopping imatinib and loss of MR$^{4.5}$ for these 3 patients was 1, 3 and 3 months. An additional 4 patients in arm A also discontinued imatinib but did not relapse. The 10 molecular relapses in arm B occurred at a median interval of 3 months (range 1–12) after randomisation. All but one patient in arm B relapsed within 7 months after randomisation. According to the ITT analysis, this results in a molecular relapse rate of 0% and 53% (95% CI 31-79%) at 6 months, 6% (95% CI 1-39%) and 60% (95% CI 37-84%) at 12 months and 21% (95% CI 7-52%) and 67% (CI 44-88%) at 24 months in arm A and arm B respectively. As-treated analysis however reveals 0% relapses in patients who continued maintenance, while for the patients who discontinued maintenance, relapse rates at 12 and 24 months since discontinuation were 56% (95% CI 37-77%) and 61% (42-81%), respectively. Five relapsing patients also had a cytogenetic relapse, one in arm A (minimal cytogenetic response) and 4 in arm B (all partial cytogenetic response). All patients in arm A who continued the allocated imatinib treatment remained in MR$^{4.5}$. No patient progressed to

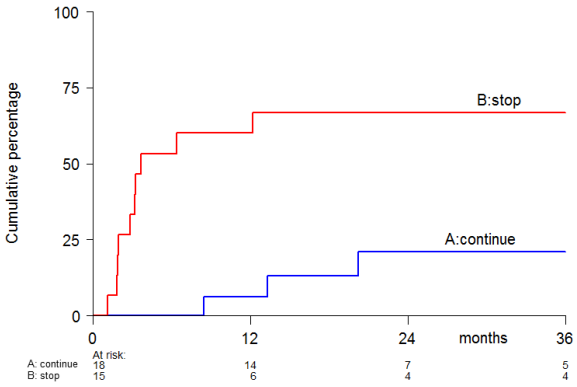


Figure 1. Time from randomization until loss of MR$^{4.5}$

accelerated phase or blast crisis. Table 1 shows the characteristics of the relapsing and non-relapsing patients restricted to the discontinued patients. Of the 5 patients in arm B who discontinued imatinib but were relapse free, all of them showed a stable $MR^{4.5}$. Of all 13 patients who lost $MR^{4.5}$, 9 restarted with imatinib in the same dose as they received before the discontinuation of imatinib. Two patients who took 600 mg imatinib before discontinuation, restarted at a dose of 800 mg imatinib, but in one patient this dose was decreased to 600 mg after 6.5 months. Another patient who took 600 mg imatinib before discontinuation, restarted at a dose of 400 mg imatinib and one patient started with nilotinib. All 13 patients regained a $MR^{4.5}$ after median 6 months (range 2-15) since reinitiation of imatinib or nilotinib. Currently, 3 patients have gone off protocol, 2 in arm A because of refusal of imatinib and adverse events and 1 in arm B because of protocol violation.

Table 1. Patient characteristics according to relapse or no relapse in the group who discontinued imatinib

	Relapsed after discontinuation		
	No	**Yes**	**Total**
Total	9	13	22
Study arm			
A: continue	4	3	7
B: stop	5	10	15
Sex (no)			
Male	7	4	11
Female	2	9	11
Sokal score (no)			
low	4	6	10
intermediate	2	5	7
high	2	2	4
unknown	1	0	1
Duration imatinib therapy (months)			
median	111	92	98
range	90-137	65-125	65-137
Time to CMR (months)			
Median	12	27	20
Range	7-26	7-60	7-60

DISCUSSION

To our knowledge, this is the first randomised trial regarding the discontinuation of imatinib in first chronic phase CML patients having achieved a durable and stable $MR^{4.5}$. Our results are encouraging: 33% of the patients in arm B who discontinued imatinib after at least 2 years of $MR^{4.5}$ did not relapse and have a long-time persistence of $MR^{4.5}$ after therapy cessation while 67% of the patients had a molecular relapse, all occurring within 7 months after cessation of imatinib. When not taking into account the intention-to-treat principle, the relapse percentage of the patients who actually discontinued imatinib was 56% at 12 months. Nevertheless and of great importance, after recommencing imatinib treatment, all evaluable relapsing patients regained an $MR^{4.5}$.

Our results are comparable with previous non-randomised stopping trials, although others included many patients who were pretreated with interferon alpha, while our patients had all received cytarabine.[4-6,8,9,13] It is unclear whether the addition of these drugs has contributed to the persistence of response after stopping imatinib.[5,14-16]

Altogether, results of the different stop studies are promising. Nevertheless, a major concern is that cessation of imatinib might lead to genomic instability due to re-exposure of leukaemic stems cells (LSCs) to BCR-ABL1 kinase activity and safety should therefore be a major issue in these studies.[17] Our and other studies show that all evaluable relapsing patients swiftly regain at least a major molecular response (MMR) after reintroduction of imatinib.[3,5,7-9] indicating that clonal shifts towards resistance against imatinib are unlikely to occur during discontinuation. However, longer follow up of these patients and larger studies are needed. Due to the limited size of the study, we were unable to determine risk factors for relapse.

It is remarkable that a subset of patients did not relapse after imatinib discontinuation, as, in vitro, imatinib or any other TKI seem to be unable to eradicate LSCs.[18-20] Indeed, several studies have shown that even in longstanding deep molecular responses with or without TKI treatment, BCR-ABL1 containing cells can still be detected and that they have persistent stem cell capacity.[13,21] Further studies focusing on discontinuation of imatinib, but also of nilotinib and dasatinib, will be highly relevant to unravel the possible molecular and immunologic mechanisms underlying sustained molecular responses or relapse. But most important for clinical practice, these studies have to define predictive factors for successful TKI discontinuation.

In conclusion, although imatinib treatment was previously expected to be life-long, our data suggest that, under close PCR monitoring, discontinuation of imatinib is safe in CML patients with a long-lasting $MR^{4.5}$. A significant part of patients will remain in $MR^{4.5}$, while relapsing patients maintain sensitivity to imatinib.

REFERENCE LIST

(1) Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349(15):1423-32.

(2) Deininger M, O'Brien S, Guilhot F, goldman J, Hochhaus A, Hughes T, et al. International Randomized Study of Interferon versus STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. Blood 2009;114:Abstract 1126.

(3) Rousselot P, Huguet F, Rea D, Legros L, Cayuela JM, Maarek O, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. Blood 2007;109(1):58-60.

(4) Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Bartley PA, et al. Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. Leukemia 2010;24(10):1719-24.

(5) Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010;11(11):1029-35.

(6) Takahashi N, Kyo T, Maeda Y, Sugihara T, Usuki K, Kawaguchi T, et al. Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia. Haematologica 2012;97(6):903-6.

(7) Cortes J, O'Brien S, Kantarjian H. Discontinuation of imatinib therapy after achieving a molecular response. Blood 2004;104(7):2204-5.

(8) Merante S, Orlandi E, Bernasconi P, Calatroni S, Boni M, Lazzarino M. Outcome of four patients with chronic myeloid leukemia after imatinib mesylate discontinuation. Haematologica 2005;90(7):979-81.

(9) Yhim HY, Lee NR, Song EK, Yim CY, Jeon SY, Shin S, et al. Imatinib mesylate discontinuation in patients with chronic myeloid leukemia who have received front-line imatinib mesylate therapy and achieved complete molecular response. Leuk Res 2012;36(6):689-93.

(10) Deenik W, van der Holt B, Verhoef GE, Smit WM, Kersten MJ, Kluin-Nelemans HC, et al. Dose-finding study of imatinib in combination with intravenous cytarabine: feasibility in newly diagnosed patients with chronic myeloid leukemia. Blood 2008;111(5):2581-8.

(11) Deenik W, Janssen JJ, van der Holt B, Verhoef GE, Smit WM, Kersten MJ, et al. Efficacy of escalated imatinib combined with cytarabine in newly diagnosed patients with chronic myeloid leukemia. Haematologica 2010;95(6):914-21.

(12) Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Kaeda J, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108(1):28-37.

(13) Ross M, Branford S Seymour J et al. Frequent and sustained drug-free remission in the Australian CML8 trial of imatinib withdrawal. Haematologica 2012;97(s1):Abstract 0189.

(14) Mahon FX, Delbrel X, Cony-Makhoul P, Faberes C, Boiron JM, Barthe C, et al. Follow-up of complete cytogenetic remission in patients with chronic myeloid leukemia after cessation of interferon alfa. J Clin Oncol 2002;20(1):214-20.

(15) Burchert A, Muller MC, Kostrewa P, Erben P, Bostel T, Liebler S, et al. Sustained molecular response with interferon alfa maintenance after induction therapy with imatinib plus interferon alfa in patients with chronic myeloid leukemia. J Clin Oncol 2010;28(8):1429-35.

(16) Preudhomme C, Guilhot J, Nicolini FE, Guerci-Bresler A, Rigal-Huguet F, Maloisel F, et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. N Engl J Med 2010;363(26):2511-21.

(17) Deininger M. Hematology: curing CML with imatinib--a dream come true? Nat Rev Clin Oncol 2011;8(3):127-8.

(18) Graham SM, Jorgensen HG, Allan E, Pearson C, Alcorn MJ, Richmond L, et al. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. Blood 2002;99(1):319-25.

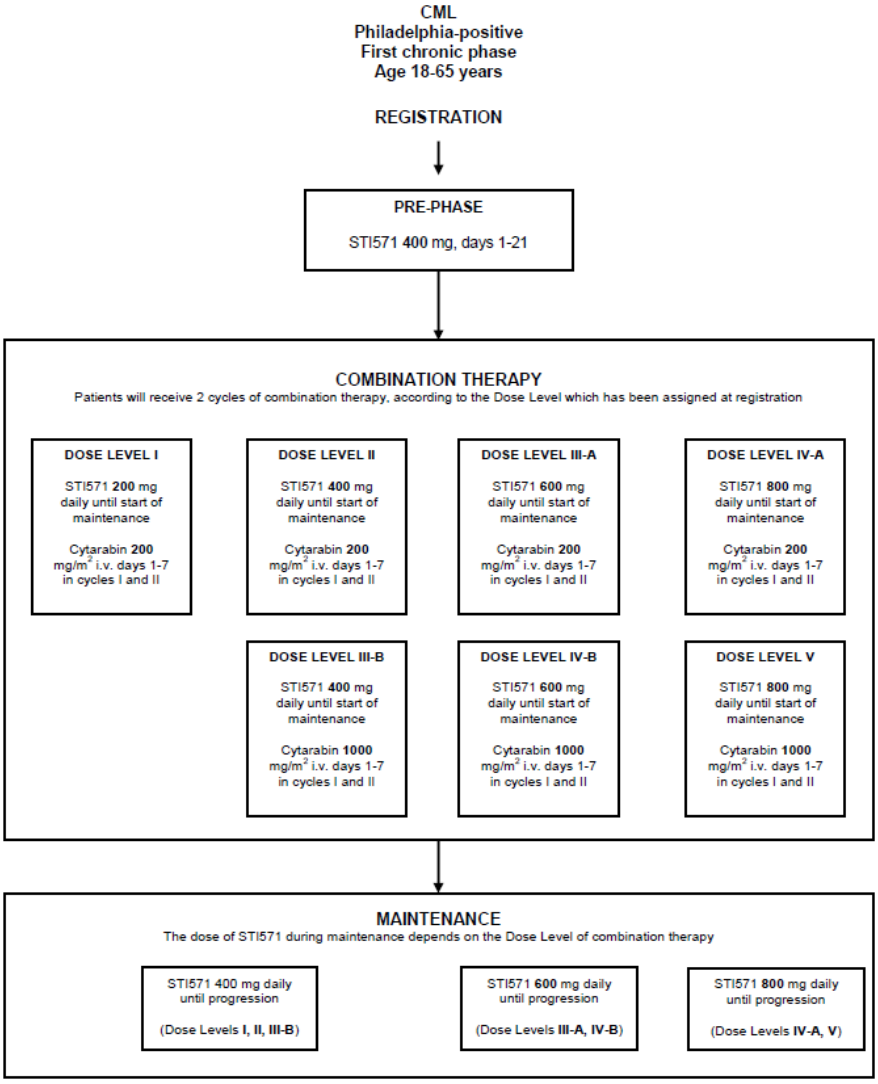
(19) Copland M, Hamilton A, Elrick LJ, Baird JW, Allan EK, Jordanides N, et al. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. Blood 2006;107(11):4532-9.

(20) Jorgensen HG, Allan EK, Jordanides NE, Mountford JC, Holyoake TL. Nilotinib exerts equipotent antiproliferative effects to imatinib and does not induce apoptosis in CD34+ CML cells. Blood 2007;109(9):4016-9.

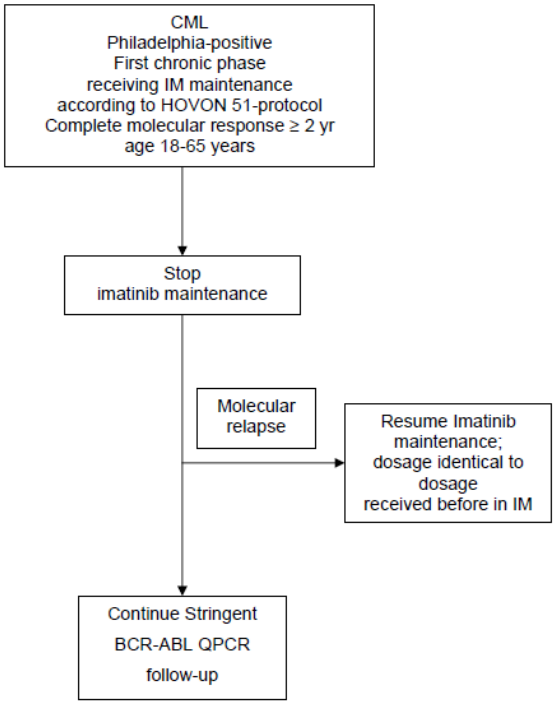
(21) Chu S, McDonald T, Lin A, Chakraborty S, Huang Q, Snyder DS, et al. Persistence of leukemia stem cells in chronic myelogenous leukemia patients in prolonged remission with imatinib treatment. Blood 2011;118(20):5565-72.

SUPPLEMENTARY FILES

Suppl. 1. Successive dose levels of cytarabine and imatinib in the HOVON 51 study



Suppl. 2. Flow diagram of imatinib stop study



Suppl. 3. Patient characteristics

	A: continue	B: stop	Total
Total	18	15	33
Sokal score (at diagnosis) (no, %)			
low	6 (33)	8 (53)	14 (42)
intermediate	5 (28)	4 (27)	9 (27)
high	5 (28)	2 (13)	7 (21)
unknown	2 (11)	1 (7)	3 (9)
Euro score (at diagnosis) (no, %)			
low	5 (28)	6 (40)	11 (33)
intermediate	10 (56)	8 (53)	18 (55)
high	1 (6)	0 (0)	1 (3)
unknown	2 (11)	1 (7)	3 (9)
Sex (no, %)			
male	9 (50%)	9 (60%)	18 (55%)
Female	9 (50%)	6 (40%)	15 (45%)
Age at entry in HOVON 51 (years)			
median	49	51	50
range	35-65	34-62	34-65
Age at randomization (years)			
median	54	56	55
range	40-72	41-67	40-72
Months from randomization in HOVON 51 and CMR			
median	19	22	20
range	3-79	7-34	3-79
Duration of CMR before randomization (months)			
median	42	44	45
range	24-63	24-72	24-72
Duration of imatinib therapy before randomization (months)			
median	67	65	65
range	39-95	37-95	37-95
Imatinib dose before randomization (mg)			
median	562	565	565
range	368-767	367-755	367-767
Cumulative imatinib dose before randomization (g)			
median	1174	951	1012
range	652-1861	631-1535	631-1861